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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/905,508	08/04/1997	LALEH SHAYESTEH	023070-06772	5513

7590 10/07/2005

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/905,508	SHAYESTEH ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/18/2005 has been entered.

2. Currently, claims 37-39 are pending in the instant application. Applicant's arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. While claim 39 was indicated as free of the art in the previous office actions, upon further review of the art, the claim is rejected as set forth below. Response to Applicant's arguments follow where appropriate. This action is NON-FINAL.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Please note, in the most recent listing of claims submitted, claim 40, which was canceled in the amendment filed 10/5/2001, is missing. In any subsequent reply to this office action,

applicant is requested to submit a complete listing of pending claims, with proper status identifiers.

Claim Rejections - 35 USC § 103

5. Claims 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonjouklian et al (hereinafter referred to as Bonjouklian; US Patent 5,378,725; 1/3/1995), in view of Arnold et al (hereinafter referred to as Arnold; Genes, Chromosomes, and Cancer, vol. 16, pages 46-54, 1996) and Volinia et al (hereinafter referred to as Volinia; Genomics, vol. 24, pp 472-477; 1994) and further in view of (in the alternative) Xiao et al (hereinafter referred to as Xiao, International Journal of Oncology; vol. 6, pp 405-411, 1995) or Skorski et al (hereinafter referred to as Skorski, Blood, vol. 86, pp 726-736, 1995).

Bonjouklian teaches and claims a method of treating PI3 kinase dependent neoplasms in mammals by administering non peptidic inhibitors (see col. 3, col. 4, table 1; col. 6, lines 49-60; and claims 1-9). Bonjouklian teaches that PI 3 kinase is an important enzyme in signal transduction with particular implications relative to the malignant transformation of cells (col. 2, lines 22-25). Bonjouklian specifically teaches a method for treating a phosphatidylinositol 3 kinase dependent condition in a mammal, such as abnormal cell growth as found in neoplasms, such as ovarian cancer, by administering a phosphatidylinositol 3 kinase inhibiting amount of a compound as shown in cols 2, 3, and 4 (col. 6, lines 49-col. 7, line 2). Bonjouklian teaches how to determine quantity of compound, such as wortmannin (an inhibitor of PI3 kinase phosphoinositide phosphorylation), to produce a desired therapeutic effect (col. 7, especially lines 54-62). It is noted that Bonjouklian do not specifically teach treating a patient with a "population of ovarian cancer cells comprising cells in which 3q26.3 is amplified", however

Bonjouklian does teach treating a "PI3 kinase dependent neoplasm" and it was known in the art at the time the invention was made that the region of chromosome 3q26 was commonly amplified in ovarian tumors as taught by Arnold (see page 49, col 2, 3q26 is increased in 42% of cases). Arnold specifically teaches that amplification of the 3q26-qter segment, which includes 3q26.3, suggests that the telomeric region of 3q contains one or more genes important in tumor initiation and/or progression (page 49, co. 2). Further, Volinia teaches that the catalytic p110 alpha subunit of PI 3 kinase (PIK3CA) is found in 3q26.3. Additionally, Xiao and Skorski teach that wortmannin, a known PI3 kinase inhibitor and taught by Bonjouklian as a treatment for a PI3 kinase dependent neoplasm, including ovarian cancer, was able to suppress growth of gastric cancer cells (see abstract of Xiao) and selectively inhibited the proliferation of leukemic cells (see pages 729 –730 and abstract of Skorski). Xiao teaches that growth of gastric cancer cell lines which exhibited elevated PI3 Kinase, MKN-45 and NUGC-4, was inhibited with wortmannin, while another gastric cancer cell line MKN-28, which did not exhibit such elevated PI 3 Kinase, was more resistant to wortmannin (see abstract, page 407, col. 2, first para, page 409, col 1 and 2). Further, Xiao teaches that the activation of PI-3 kinase appears to be required for oncogenic growth of these cells (see abstract). Skorski teaches that wortmannin inhibited the growth of leukemic cells (CML) which require PI 3 kinase for proliferation (see abstract, page 731, col. 2, lines 20-24).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the PI3 kinase inhibitor wortmannin to treat ovarian cancer as taught by Bonjouklian, and to include treatment of ovarian cancer cells which had regions of chromosome 3q26, including 3q26.3, amplified as Arnold taught that such region was commonly

amplified in ovarian tumors. Further, Volinia teaches that PIK3CA was found in 3q26.3. Therefore, from the combined teachings of Volinia and Arnold, the ordinary artisan would been taught that ovarian cancer tumors would include those that had the region 3q26 amplified, and that PIK3CA was found in the same region, particularly 3q26.3. Given that the Bonjouklian patent is directed to treatment of PI3 kinase dependent neoplasms, such as ovarian cancer, the ordinary artisan would have been motivated to include ovarian tumors which were characterized by the amplification of a chromosomal region containing a PI3 kinase in the method of Bonjouklian because it was known in the art that PIK3CA was found at 3q26.3 and therefore would have been obvious to the ordinary artisan that amplification of 3q26, a region containing a PI 3 kinase would result in elevated PIK3CA. The ordinary artisan would have had a reasonable expectation of success that wortmannin, as taught by Bonjouklian, would be an effective inhibitor of the pathological proliferation of ovarian tumor cells which had the region 3q26 amplified because wortmannin was known to inhibit growth of different cancerous cells which had elevated PI 3 kinase activity and were PI 3 Kinase dependent as taught by Xiao and Skorski.

It is noted that claim 37 has been amended to recite "a population of ovarian cancer cells that has been determined to comprise cancer cells in which 3q26.3 has been amplified...". It appears that the amendment intends for a step of determining or identifying specific cells prior to the administration of PI3 kinase inhibitors in the method of treating cancer cells. While there is currently no positive active step of detection or identification in the claimed method, even if there were, it would have been further prima facie obvious to one of ordinary skill in the art at the time the invention was made to identify or detect ovarian cancer cells which had 3q26.3 amplified in the method of treating PI3 kinase dependent ovarian cancer as taught by

Bonjouklian for the purpose of identifying ovarian cancer cells for treatment because Arnold teaches that in 42% of ovarian cancer cells, the region of 3q26 is amplified and specifically teaches amplification of 3q26-qter, which includes 3q26.3, therefore demonstrates that amplification of the 3q26 region is a marker for some ovarian cancers. The ordinary artisan would have been motivated to determine that the region of 3q26, including 3q26.3, was amplified for the purpose of validating that an ovarian cell population contained ovarian cancer cells in the method of treatment of Bonjouklian. Additionally, as Arnold teaches that amplification of 3q26-qter is a marker for ovarian cancer and Volinia teaches that this region contains PIK3CA, a PI3 kinase target which Bonjouklian teaches to inhibit, the ordinary artisan would reasonably expect that ovarian cancers with the 3q26 region amplified would contain amplification of PIK3CA. As Xiao teaches that growth of gastric cancer cells which had elevated PI3 kinase activity was suppressed with the PI3 kinase inhibitor wortmannin (which is the preferred inhibitor taught by Bonjouklian), the ordinary artisan would be motivated to identify ovarian cancer cells which would have elevation of PI3 kinase activity in the method of treatment of PI3 kinase dependent ovarian cancer of Bonjouklian, because the prior art at the time the invention was made demonstrated that inhibition of cancer cells which showed elevation of PI3 kinase activity could be achieved effectively by inhibiting a PI3 kinase. The ordinary artisan, given the teachings of Arnold, Volinia, and Xiao or Skorski, would reasonably expect that proliferation of ovarian cancer cells in which 3q26.3 was amplified would be effectively inhibited with the inhibitor used by Bonjouklian (which targets PI3 kinases).

Response to Arguments

6. The response traverses the rejection. The response asserts that neither Xiao nor Skorski teach inhibition of ovarian cancer cells and that the references focus on the 85 kd subunit expression and not the 110 kd subunit. These arguments have been thoroughly reviewed but were not found persuasive. Xiao and Skorski both teach that inhibition of PI 3 kinase with wortmannin inhibited the pathological proliferation of different PI 3 kinase dependent cancer cells and provide a reasonable expectation of success that wortmannin can be used to inhibit different types of cancer cells with elevated PI 3 kinase activity. Further both references show that inhibition of the 110 kd subunit by wortmannin inhibits PI 3 kinas activity which is elevated in the cancer cells taught by Xiao or required for proliferation of the CML cells taught by Skorski.

The response asserts that Schultz et al studied the cytotoxic effects of wortmannin on different cancer cell lines in vitro and the antitumor effects in mouse tumors in vivo and human carcinoma xenografts in vivo, and found that in vivo anti tumor activity did not correlate with in vitro sensitivity. The response asserts that the teaching of Schultz indicate that the findings of Xiao and Skorski would do not provide a reasonable expectation of success that wortmannin would be effective for inhibition of the pathological proliferation of ovarian cancer cells. This argument as well as the teachings of Schultz have been thoroughly reviewed but were not found persuasive. While acknowledging that wortmannin is a PI3 kinase inhibitor, Schultz does not teach if the PI 3 kinase activity of the cancer cell lines, tumors, or xenografts was elevated or whether growth of any of these cells was PI 3 kinase dependent, as is addressed by the teachings of Xiao and Skorski, respectively. Additionally, Schultz acknowledges that further studies are

needed to determine whether levels of PI3 kinase in the various cells lines correlate with wortmannin susceptibility (see page 1138, col. 1, first full para). Applicants comments with regard to the teachings of Schultz that "in vivo antitumor activity was not observed with two human cell lines having the greatest sensitivity to wortmannin in vitro" is unclear. It appears that applicants are suggesting that it was unpredictable that wortmannin would have in vivo antitumor activity despite displaying in vitro inhibitory activity, whereas the scope of the instantly pending claims broadly encompass use of any PI 3 kinase inhibitor to inhibit the pathological proliferation of cancer cells in vivo, which includes wortmannin, while applicants own specification only demonstrates *in vitro* sensitivity of ovarian cancer cells with LY294002. A thorough review of the prior art, however, supports the predictability of the inhibition of PI 3 kinase dependent cancer cell proliferation, both in vitro and in vivo, with wortmannin, given the teachings of Skorski and Xiao, as well as the teachings and claims of the Bonjouklian patent. Furthermore, a large number of PI 3 kinase inhibitors were known at the time the invention was made and known to inhibit PI 3 kinase activity, and PI 3 kinase dependent cell growth.

The response asserts that the combination of Bonjouklian, Arnold, and Volinia is deficient because it does not teach that 3q26.3 is amplified in ovarian cancer cells and that Bonjouklian is silent with regard to what constitutes a PI 3 kinase dependent ovarian tumor. These arguments have been thoroughly reviewed but were not found persuasive. Firstly, Arnold teaches that a large segment of 3q is amplified, specifically 3q26-qter (page 49, col. 2, last para,) which includes 3q26.3. Therefore, Arnold teaches that the region of amplification commonly found in ovarian cancer cells included 3q26.3. Secondly, The Bonjouklian patent claims a method for treating PI-3 kinase dependent neoplasms and teaches that PI 3 kinase is an important

enzyme in signal transduction with particular implications relative to the malignant transformation of cells. This teaching, coupled with the prior art demonstration that cancer cells which exhibited *elevated* PI 3 kinase (Xiao) or where proliferation was PI 3 kinase dependent (Xiao and Skorski) were effectively inhibited with a PI 3 kinase inhibitor, would have given the ordinary artisan a teaching of what constituted a PI 3 kinase dependent neoplasm. The fact that Bonjouklian does not specifically teach administration to patients with ovarian cancers characterized by 'amplification of 3q26.3', does not negate the fact that one of ordinary skill in the art would be motivated to include such administration to patients with 3q26.3 amplified given that it was well known in the art that the region of 3q26-qter was amplified in ovarian tumors and that PI3 kinase was found on 3q26.3. The link for treatment of ovarian cancers in which 3q26.3 is amplified with PI3kinase inhibitors is provided by Bonjouklian which teaches treatment of PI3 kinase dependent neoplasms such as ovarian cancers, Arnold which teaches that the 3q26 region is amplified in 42% of ovarian cancers, Volinia which teaches the localization of PIK3CA to 3q26.3, and Xiao and Skorski which teach inhibition of cancer cell growth with a PI 3 kinase inhibitor in cancer cells exhibiting elevated PI 3 kinase and PI 3 kinase dependent proliferation. Although Arnold does not teach any candidate genes known in the region, it was known in the art at the time the invention as made that PI3 kinase was localized to this region of chromosome 3. Volinia teaches that PIK3CA is found in the region that Arnold teaches is amplified in ovarian cancers. For these reasons, the rejection is maintained.

7. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bonjouklian, in view of Arnold and Volinia, and further in view of Xiao or Skorski, as applied to claims 37 and

38 above, and further in view of Powis (Powis et al; International Journal of Pharmacognosy, vol. 33, pages 17-26, 1995).

The teachings of Bonjouklian, Volinia, Arnold, Xiao and Skorski are set forth above. Bonjouklian & Arnold & Volinia in view of Xiao or Skorski do not teach the PI 3 kinase inhibitor LY294002 for the inhibition of the pathological proliferation of ovarian cancer cells, although Xiao does teach that LY294002 is a PI 3 kinase inhibitor. However, Powis teaches that LY294002 is a selective PI 3 kinase inhibitor (page 20, col. 1, last sentence of first full para). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use LY294002 to inhibit PI 3 kinase activity in the method of Bonjouklian & Arnold & Volinia in view of Xiao or Skorski. The ordinary artisan would have been motivated to use LY294002 to inhibit PI 3 kinase activity in the method of Bonjouklian & Arnold & Volinia in view of Xiao or Skorski because it was known to be a selective inhibitor of PI 3 kinase activity as taught by Powis. The ordinary artisan would have had a reasonable expectation of success that LY294002 could be used to inhibit the pathological proliferation of ovarian cancer cells in the method of Bonjouklian & Arnold & Volinia in view of Xiao or Skorski because LY294002 was known to be an effective inhibitor of PI 3 kinase.

8. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bonjouklian, in view of Arnold and Volinia, and further in view of Xiao or Skorski, as applied to claims 37 and 38 above, and further in view of June (US Patent 6632789).

The teachings of Bonjouklian, Volinia, Arnold, Xiao and Skorski are set forth above. Bonjouklian & Arnold & Volinia in view of Xiao or Skorski do not teach the PI 3 kinase

inhibitor LY294002 for the inhibition of the pathological proliferation of ovarian cancer cells, although Xiao does teach that LY294002 is a PI 3 kinase inhibitor. However, June teaches that LY294002 is a preferred PI 3 kinase inhibitor (col. 5, lines 60-62) and teaches inhibiting a response, such as proliferation, by a T cell, using LY294002 (claims 1-19). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use LY294002 to inhibit PI 3 kinase activity in the method of Bonjouklian & Arnold & Volinia in view of Xiao or Skorski. The ordinary artisan would have been motivated to use LY294002 to inhibit PI 3 kinase activity in the method of Bonjouklian & Arnold & Volinia in view of Xiao or Skorski because it was known to be a preferred inhibitor of PI 3 kinase activity as taught by June. The ordinary artisan would have had a reasonable expectation of success that LY294002 could be used to inhibit the pathological proliferation of ovarian cancer cells in the method of Bonjouklian & Arnold & Volinia in view of Xiao or Skorski because LY294002 was known to be an effective inhibitor of PI 3 kinase activity.

9. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bonjouklian, in view of Arnold and Volinia, and further in view of Xiao or Skorski, as applied to claims 37 and 38 above, and further in view Lavin (Lavin et al; Experientia, vol. 52, pages 979-994, 1996).

The teachings of Bonjouklian, Volinia, Arnold, Xiao and Skorski are set forth above. Bonjouklian & Arnold & Volinia in view of Xiao or Skorski do not teach the PI 3 kinase inhibitor LY294002 for the inhibition of the pathological proliferation of ovarian cancer cells, although Xiao does teach that LY294002 is a PI 3 kinase inhibitor. However, Lavin teaches that LY294002 is an effective PI 3 kinase inhibitor and abrogated the ability of NGF to prevent

apoptosis in PC-12 cells, suggesting one important role of PI 3 kinase is to ensure cell survival by preventing apoptosis (986, col. 2, lines 18-25). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use LY294002 to inhibit PI 3 kinase activity in the method of Bonjouklian & Arnold & Volinia in view of Xiao or Skorski. The ordinary artisan would have been motivated to use LY294002 to inhibit PI 3 kinase activity in the method of Bonjouklian & Arnold & Volinia in view of Xiao or Skorski because it was known to be a selective inhibitor of PI 3 kinase and cell growth as taught by Lavin. The ordinary artisan would have had a reasonable expectation of success that LY294002 could be used to inhibit the pathological proliferation of ovarian cancer cells in the method of Bonjouklian & Arnold & Volinia in view of Xiao or Skorski because LY294002 was known to be an effective inhibitor of PI 3 kinase and to abrogate the ability of a growth factor to prevent apoptosis.

Conclusion

10. No claims are allowable over the cited prior art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jehanne Sitton
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Art Unit 1634
Sept 30, 2005